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IBM Technical Disclosure Bulletins

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Today's Date: 6/14/2001

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USPT,PGPB,JPAB,EPAB,DWPI	Cpg	2619	L2
USPT,PGPB,JPAB,EPAB,DWPI	Iga or mucosal	14458	L1

WO 96/02555

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L4: Entry 1 of 1 File: USPT Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6218371 B1
TITLE: Methods and products for stimulating the immune system using immunotherapeutic oligonucleotides and cytokines

DEPR:
The subject is exposed to the antigen. As used herein, the term "exposed to" refers to either the active step of contacting the subject with an antigen or the passive exposure of the subject to the antigen in vivo. Methods for the active exposure of a subject to an antigen are well-known in the art. In general, an antigen is administered directly to the subject by any means such as intravenous, intramuscular, oral, transdermal, mucosal, intranasal, intratracheal, or subcutaneous administration. The antigen can be administered systemically or locally. Methods for administering the antigen and the CpG and immunopotentiating cytokine are described in more detail below. A subject is passively exposed to an antigen if an antigen becomes available for exposure to the immune cells in the body. A subject may be passively exposed to an antigen, for instance, by entry of a foreign pathogen into the body or by the development of a tumor cell expressing a foreign antigen on its surface. When a subject is passively exposed to an antigen it is preferred that the CpG oligonucleotide is an oligonucleotide of 8-100 nucleotides in length and/or has a phosphate modified backbone.

DEPR:
For use in therapy, an effective amount of an appropriate CpG oligonucleotide and immunopotentiating cytokine alone or formulated as a nucleic acid/cytokine delivery complex can be administered to a subject by any mode allowing the oligonucleotide to be taken up by the appropriate target cells (e.g. dendritic cells). Preferred routes of administration include but are not limited to oral, transdermal (e.g. via a patch), injection (subcutaneous, intravenous, parenteral, intraperitoneal, intrathecal, etc.), intranasal, intratracheal, and mucosal. An injection may be in a bolus or a continuous infusion.

(FILE 'HOME' ENTERED AT 17:38:20 ON 14 JUN 2001)

FILE 'MEDLINE, CAPLUS, BIOTECHDS, CANCERLIT, EMBASE' ENTERED AT 17:38:55 ON 14 JUN 2001

L1 10 S CPG MOTIF AND (MUCOSAL OR IGA)

L2 8 DUP REM L1 (2 DUPLICATES REMOVED)

L2 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2001 ACS

AN 2001:247187 CAPLUS

DN 134:275762

TI Immunostimulatory nucleic acids

IN Krieg, Arthur M.; Schetter, Christian; Vollmer, Jorg

PA University of Iowa Research Foundation, USA; Coley Pharmaceutical G.b.m.H.

SO PCT Int. Appl., 338 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001022972	A2	20010405	WO 2000-US26383	20000925

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-156113 P 19990925
US 1999-156135 P 19990927
US 2000-227436 P 20000823

OS MARPAT 134:275762

AB The invention relates to immunostimulatory nucleic acid compns. and methods of using the compns. The T-rich nucleic acids contain poly T sequences and/or have greater than 25% T nucleotide residues. The TG nucleic acids have TG dinucleotides. The C-rich nucleic acids have at least one poly-C region and/or greater than 50% C nucleotides. These immunostimulatory nucleic acids function in a similar manner to nucleic acids contg. CpG motifs. The invention also encompasses preferred CpG nucleic acids.

L2 ANSWER 2 OF 8 BIOTECHDS COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 2001-03307 BIOTECHDS

TI Oligonucleotide containing CpG motifs enhances immune response to mucosally or systemically administered tetanus toxoid; vaccine adjuvant

AU Eastcott J W; Holmberg C J; Dewhirst F E; Esch T R; Smith D J; *Taubman M A

CS Forsyth-Inst.Boston

LO Department of Immunology, The Forsyth Institute, 140 Fenway, Boston, MA 02115, USA.

Email: mtaubman@forsyth.org
SO Vaccine; (2001) 19, 13-14, 1636-42
CODEN: VACCDE ISSN: 0264-410X
DT Journal
LA English
AB Oligonucleotides containing unmethylated CpG dinucleotides induce proliferation of B-lymphocytes and activation of macrophages and thus stimulate the immune system. An oligonucleotide containing an unmethylated CpG dinucleotide flanked by 2 5'-purines and 2 3'-pyrimidines was tested for the ability to affect antibody levels to tetanus toxoid. Groups of male Rowett rats (5-6 per group) were given colloidal aluminum hydroxide alone or with tetanus toxoid bound to the aluminum hydroxide, or with tetanus toxoid plus CpG oligonucleotide. Antigens were given s.c. in salivary gland once, or by gastric intubation on 3 consecutive days. On day 124, all animals were boosted with the same antigen given in the same way. Serum IgG and saliva ***IgA*** antibody to tetanus toxoid was determined by ELISA. Serum antibody levels were higher in oligonucleotide plus tetanus toxoid treated rats regardless of administration route. An oligonucleotide with unmethylated CpG motifs plus an immunogen bound to Al(OH)3 can give enhanced specific antibody when given intragastrically or s.c. (30 ref)

L2 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2001 ACS
AN 2000:719793 CAPLUS
DN 134:339289
TI Oral, intrarectal and intranasal immunizations using CpG and non-CpG oligodeoxynucleotides as adjuvants
AU McCluskie, M. J.; Davis, H. L.
CS Loeb Health Research Institute at the Ottawa Hospital, Ottawa, K1Y 4E9, Can.
SO Vaccine (2000), 19(4-5), 413-422
CODEN: VACCDE; ISSN: 0264-410X
PB Elsevier Science Ltd.
DT Journal
LA English
AB We have previously demonstrated that synthetic oligodeoxynucleotides (ODN) contg. immunostimulatory CpG motifs (CpG ODN) are potent adjuvants in mice when delivered by i.m., intranasal and s.c. routes. Herein, using tetanus toxoid (TT) as a model antigen in BALB/c mice, we compared the ability of CpG ODN to induce ***mucosal*** and systemic humoral immune responses when antigen was delivered by three different routes: intrarectal, intranasal and oral. Results showed differences in immune responses with the three routes and also revealed that non-CpG "control" ODN had adjuvant effects when used at ***mucosal*** sites. This was unexpected since non-CpG ODN do not have such immunostimulatory effects in vitro or after parenteral immunization. These findings were further investigated after oral delivery of a killed influenza vaccine on its own as well as combined with TT and hepatitis B surface antigen. Our findings demonstrate that with ***mucosal*** delivery, there is a Th2 immunostimulatory effect assocd. with the phosphorothioate ODN backbone, and that the presence of CpG motifs shifts this towards a Th1 response.
RE.CNT 39
RE
(1) Abreu-Martin, M; Crit Rev Immunol 1996, V16, P277 CAPLUS
(2) Beagley, K; Crit Rev Immunol 1998, V18, P237 CAPLUS
(3) Cheng, E; Vaccine 1999, V18, P38 CAPLUS

(4) Chu, R; J Exp Med 1997, V186, P1623 CAPLUS
(5) Davis, H; J Immunol 1998, V160, P870 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2001 ACS
AN 2000:124491 CAPLUS
DN 133:118566
TI Immunostimulatory-sequence DNA is an effective ***mucosal*** adjuvant
AU Horner, A. A.; Raz, E.
CS Department of Medicine and The Sam and Rose Stein Institute for Aging, University of California, San Diego, CA, 92093-0663, USA
SO Curr. Top. Microbiol. Immunol. (2000), 247(Immunobiology of Bacterial CpG-DNA), 185-198
CODEN: CTMIA3; ISSN: 0070-217X
PB Springer-Verlag
DT Journal; General Review
LA English
AB A review with 36 refs. on immunostimulatory-sequence (ISS) DNA contg. the ***CpG*** ***motif*** as an ***mucosal*** adjuvant, the ***mucosal*** immune system, and effects of ISS DNA on ***mucosal*** immunization.
RE.CNT 36
RE
(2) Anitescu, M; J Interferon Cytokine Res 1997, V17, P781 CAPLUS
(3) Ballas, Z; J Immunol 1996, V157, P1840 CAPLUS
(4) Berlin, C; Cell 1993, V74, P185 CAPLUS
(7) Davis, H; J Immunol 1998, V160, P870 CAPLUS
(8) Defrance, T; J Exp Med 1992, V175, P671 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2001 ACS
AN 2000:124490 CAPLUS
DN 133:118565
TI Use of CpG DNA for enhancing specific immune responses
AU Davis, H. L.
CS Loeb Health Research Institute, Ottawa, ON, KIY 4E9, Can.
SO Curr. Top. Microbiol. Immunol. (2000), 247(Immunobiology of Bacterial CpG-DNA), 171-183
CODEN: CTMIA3; ISSN: 0070-217X
PB Springer-Verlag
DT Journal; General Review
LA English
AB A review with 68 refs. on adjuvant properties of CpG DNA, role of ***CpG*** ***motif*** in DNA vaccines, effects of CpG DNA on antigen activity of protein antigens, CpG DNA as a ***mucosal*** adjuvant, Th1 cells effect on immune activity of CpG DNA, and CpG DNA and antigen-antibody complexes.
RE.CNT 68
RE
(1) Ballas, Z; J Immunol 1996, V157, P1840 CAPLUS
(2) Barrios, C; Eur J Immunol 1996, V26, P1489 CAPLUS
(3) Bird, A; Trends in Genetics 1987, V3, P342 CAPLUS
(4) Boggs, R; Antisense Nucl Acid Drug Develop 1997, V7, P461 CAPLUS
(6) Broide, D; J Immunol 1998, V161, P7054 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2001 ACS
AN 1999:763900 CAPLUS
DN 132:11626
TI CpG oligonucleotides and other adjuvants for inducing ***mucosal*** immunity
IN McCluskie, Michael J.; Davis, Heather L.
PA Loeb Health Research Institute At the Ottawa Hospital, Can.; CPG Immunopharmaceuticals, Inc.
SO PCT Int. Appl., 116 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9961056	A2	19991202	WO 1999-US11359	19990521
WO 9961056	A3	20000406		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9941977	A1	19991213	AU 1999-41977	19990521
EP 1077722	A2	20010228	EP 1999-925754	19990521
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRAI US 1998-86393 P 19980522
WO 1999-US11359 W 19990521
AB The authors disclose the use of immunostimulatory oligonucleotides contg. a ***CpG*** ***motif*** for inducing ***mucosal*** immunity. The CpG immunostimulatory oligonucleotides may be administered alone or in combination with antigen and/or with other adjuvants. In one example, mice were immunized with hepatitis B virus S protein aerosol in conjunction with either cholera toxin or CpG oligonucleotide. A local and systemic IgG response was obsd. using either adjuvant; cholera toxin in combination with CpG oligonucleotide induced a distant ***mucosal*** (sIgA) response. In addn., these adjuvants induced a cytotoxic T-cell response to the antigen that was not obsd. on immunization with antigen alone.

L2 ANSWER 7 OF 8 MEDLINE DUPLICATE 1
AN 1999242528 MEDLINE
DN 99242528 PubMed ID: 10224473
TI DNA-Based immunization for asthma.
AU Broide D; Raz E
CS University of California San Diego, Department of Medicine, La Jolla, CA, USA.. dbroide@ucsd.edu
NC AI33977 (NIAID)
AI38425 (NIAID)
AI40682 (NIAID)
+

SO INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (1999 Feb-Apr) 118 (2-4)
453-6.
Journal code: BJ7; 9211652. ISSN: 1018-2438.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199906
ED Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990610
AB BACKGROUND: Immunostimulatory DNA sequences (ISS) containing a ***CpG*** ***motif*** are able to inhibit Th2-mediated airway eosinophilia and bronchial hyperresponsiveness in a mouse model of asthma. METHODS: To determine the optimal frequency and timing of intervention with ISS in inhibiting Th2 cytokine production and airway eosinophilia, we used ISS administration protocols which differed in the frequency (one vs. two doses), route (systemic vs. ***mucosal***) and timing of ISS administration (before or together with antigen) in a mouse model of ovalbumin-induced eosinophilic airway inflammation. RESULTS: ISS induced Th1 cytokine production (IFN-gamma) and effectively inhibited Th2 cytokine production (IL-5) as well as eosinophilic inflammation when ISS was administered before or coadministered with inhaled allergen challenge. Although ISS was effective when coadministered with inhaled allergen, it was most effective when administered once 6 days prior to allergen challenge. ***Mucosal*** (intranasal and intratracheal) delivery of ISS was as effective as systemic (intraperitoneal) ISS delivery in inhibiting airway eosinophilia and switching cytokine responses from a Th2 to a Th1 response. CONCLUSIONS: ISS is most effective in inhibiting airway eosinophilia when administered as a single dose 6 days prior to antigen inhalation. However, ISS can also significantly inhibit eosinophilic inflammation, when coadministered with antigen inhalation. Thus, ISS administered prior or together with allergen should be considered as a novel method of allergen-based immunotherapy.

L2 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2001 ACS
AN 1998:476951 CAPLUS
DN 129:243795
TI CpG DNA, a novel immune enhancer for systemic and ***mucosal*** immunization with influenza virus
AU Moldoveanu, Zina; Love-Homan, Laurie; Huang, Wen Qiang; Krieg, Arthur M.
CS Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL, 35294-2170, USA
SO Vaccine (1998), 16(11/12), 1216-1224
CODEN: VACCDE; ISSN: 0264-410X
PB Elsevier Science Ltd.
DT Journal
LA English
AB Bacterial DNA causes B cell proliferation, Ig secretion, and Th1-like cytokine secretion, due to unmethylated CpG dinucleotides in particular base contexts (CpG motifs), which are far more common in bacterial DNA than in vertebrate DNA. Synthetic oligodeoxynucleotides (ODN) contg. CpG motifs also trigger immune activation, suggesting possible utility as vaccine enhancers. Mice systemically primed with formalin-inactivated influenza virus mixed with CpG ODN, generated virus-specific serum

antibodies at titers approx. 7-fold higher than mice immunized without CpG; the titers were further increased following an identical second injection. To det. whether CpG could be absorbed through mucosae and enhance vaccination responses, mice were immunized intranasally (IN) with the same prepn. of virus with or without CpG ODN or Escherichia coli DNA. Following IN immunization, CpG ODN or E. coli DNA promoted increased prodn. of influenza-specific antibodies in serum, saliva, and the genital tract, compared with the control groups. Thus, stimulatory CpG ODN are promising new immune enhancers for vaccination applications.